Note that the generation of T cells and/or antibodies can also be accomplished by administering cells, preferably treated to be rendered non-proliferative, which present relevant T cell or B cell epitopes for response, such as the epitopes discussed supra.

The therapeutic approaches may also include antisense therapies, wherein an antisense molecule, preferably from 10 to 100 nucleotides in length, is administered to the subject either "neat" or in a carrier, such as a liposome, to facilitate incorporation into a cell, followed by inhibition of expression of the protein. Such antisense sequences may also be incorporated into appropriate vaccines, such as in viral vectors (e.g., Vaccinia), bacterial constructs, such as variants of the known BCG vaccine, and so forth.

Other features and applications of the invention will be clear to the skilled artisan, and need not be set forth herein. The terms and expression which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expression of excluding any equivalents of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

We claim:

1. Isolated nucleic acid molecule which encodes a cancer associated antigen, whose amino acid sequence is identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 3, 4, 8, 15, 19, 22, or 26.

2. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 1.

3. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 3.

4. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 4.

5. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 8.

6. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 15.

7. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 19.

8. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 22.

9. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 26.

10. Expression vector comprising the isolated nucleic acid molecule of claim 1, operably linked to a promoter.

11. Eukaryotic cell line or prokaryotic cell strain, transformed or transfected with the expression vector of claim 10.

12. Isolated cancer associated antigen comprising all or part of the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15, 19, 22 or 26.

13. Eukaryotic cell line or prokaryotic cell strain, transformed or transfected with the isolated nucleic acid molecule of claim 1.

14. The eukaryotic cell line or prokaryotic cell strain of claim 13, wherein said cell line is also transfected with a nucleic acid molecule coding for a cytokine.

15. The eukaryotic cell line or prokaryotic cell strain of claim 14, wherein said cell line is further transfected by a nucleic acid molecule coding for an MHC molecule.

16. The eukaryotic cell line or prokaryotic cell strain of claim 14, wherein said cytokine is an interleukin.

17. The eukaryotic cell line or prokaryotic cell strain of claim 16, wherein said interleukin is IL-2, IL-4 or IL-12.

18. The eukaryotic cell line or prokaryotic cell strain of claim 13, wherein said cell line has been rendered non-proliferative.

19. The eukaryotic cell line of claim 13, wherein said cell line is a fibroblast cell line.

20. Expression vector comprising a mutated or attenuated virus and the isolated nucleic acid molecule of claim 1.

21. The expression vector of claim 20, wherein said virus is adenovirus or vaccinia virus.

22. The expression vector of claim 21, wherein said virus is vaccinia virus.

23. The expression vector of claim 21, wherein said virus is adenovirus.

24. Expression system useful in transfecting a cell, comprising (i) a first vector containing a nucleic acid molecule which codes for the isolated cancer associated antigen of claim 13 and (ii) a second vector selected from the group consisting of (a) a vector containing a nucleic acid molecule which codes for an MHC or HLA molecule which presents an antigen derived from said cancer associated antigen and (b) a vector containing a nucleic acid molecule which codes for an interleukin.

25. Immunogenic composition comprising the isolated cancer antigen of claim 12, and a pharmaceutically acceptable adjuvant.

26. The immunogenic composition of claim 25, wherein said adjuvant is a cytokine, a saponin, or GM-CSF.

27. Immunogenic composition comprising at least one peptide consisting of an amino acid sequence of from 8 to 12 amino acids concatenated to each other in the isolated cancer associated cancer antigen of claim 12, and a pharmaceutically acceptable adjuvant.

28. The immunogenic composition of claim 27, wherein said adjuvant is a saponin, a cytokine, or GM-CSF.

29. The immunogenic composition of claim 25, wherein said composition comprises a plurality of peptides which complex with a specific MHC molecule.

30. Immunogenic composition which comprises at least one expression vector which encodes a peptide derived from the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15, 19, 22 or 26.

31. The immunogenic composition of claim 30, wherein said at least one expression vector codes for a plurality of peptides.

32. Vaccine useful in treating a subject afflicted with a cancerous condition comprising the isolated eukaryotic cell line of claim 13 and a pharmacologically acceptable adjuvant.

33. The vaccine of claim 32, wherein said eukaryotic cell line has been rendered non-proliferative.

34. The vaccine of claim 33, wherein said eukaryotic cell line is a human cell line.

35. A composition of matter useful in treating a cancerous condition comprising a non-proliferative cell line having expressed on its surface a peptide derived from the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15, 19, 22 or 26.

36. The composition of matter of claim 35, wherein said cell line is a human cell line.

37. A composition of matter useful in treating a cancerous condition, comprising (i) a peptide derived from the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15, 19, 22 or 26, (ii) an MHC or HLA molecule, and (iii) a pharmaceutically acceptable carrier.

38. Isolated antibody which is specific for the cancer associated antigen of claim 12.

39. The isolated antibody of claim 38, wherein said antibody is a monoclonal antibody.

40. Method for screening for cancer in a sample, comprising contacting said sample with a nucleic acid molecule which hybridizes to all or part of the molecule encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15, 19, 22 or 26 and determining hybridization as an indication of cancer cells in said sample.

41. A method for screening for cancer in a sample, comprising contacting said sample with the isolated antibody of claim 38, and determining binding of said antibody to a target as an indicator of cancer.

42. Method for diagnosing a cancerous condition in a subject, comprising contacting an immune reactive cell containing sample of said subject to a cell line transfected with the isolated nucleic acid molecule of claim 1, and determining interaction of said transfected cell line with said immunoreactive cell, said interaction being indicative of said cancer condition.

43. A method for determining regression, progression of onset of a cancerous condition comprising monitoring a sample from a patient with said cancerous condition for a parameter selected from the group consisting of (i) a protein encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15, 19, 22 or 26, (ii) a peptide derived from said protein, (iii) cytolytic T cells specific for said peptide and an MHC molecule with which it non-covalently complexes, and (iv) antibodies specific for said CT protein, wherein amount of said parameter is indicative of progression or regression or onset of said cancerous condition.

44. The method of claim 43, wherein said sample is a body fluid or exudate.

45. The method of claim 43, wherein said sample is a tissue.

46. The method of claim 43, comprising contacting said sample with an antibody which specifically binds with said protein or peptide.

47. The method of claim 46, wherein said antibody is labelled with a radioactive label or an enzyme.

48. The method of claim 46, wherein said antibody is a monoclonal antibody.

49. The method of claim 43, comprising amplifying RNA which codes for said protein.

50. The method of claim 49, wherein said amplifying comprises carrying out polymerase chain reaction.

51. The method of claim 42, comprising contacting said sample with a nucleic acid molecule which specifically hybridizes to a nucleic acid molecule which codes for or expresses said protein.

52. The method of claim 49, wherein said nucleic acid molecule comprises SEQ ID NO: 9, 10, 11, 12, 13, 14, 17, 18, 20, 21, 24, 25, 28 or 29.

53. The method of claim 43, comprising assaying said sample for shed protein.

54. The method of claim 43, comprising assaying said sample for antibodies specific for said protein, by contacting said sample with protein.

55. Method for diagnosing a cancerous condition comprising assaying a sample taken from a subject for an immunoreactive cell specific for a peptide derived from a protein encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15, 19, 22 or 26, complexed to an MHC molecule, presence of said immunoreactive cell being indicative of said cancerous condition.

56. Composition comprising at least one peptide consisting of an amino acid sequence of from 8 to 25 amino acids concatenated to each other in the isolated cancer associated antigen of claim 12, and a pharmaceutically acceptable adjuvant.

57. The composition of claim 56, wherein said adjuvant is a saponin, a cytokine, or GM-CSF.

58. The composition of claim 56, comprising a plurality of MHC binding peptides.

59. Composition comprising an expression vector which encodes at least one peptide consisting of an amino acid sequence of from 8 to 25 amino acids concatenated to each other in the isolated cancer associated antigen of claim 12, and pharmaceutically acceptable adjuvant.

60. The composition of claim 59, wherein said expression vector encodes a plurality of peptides.

61. A method for screening for possible presence of a pathological condition, comprising assaying a sample from a patient believed to have a pathological condition for antibodies specific to at least one of the cancer associated antigens encoded by SEQ ID NOS: 1, 2, 3, 4, 8, 15, 19, 22 or 26, presence of said antibodies being indicative of possible presence of said pathological condition.

62. The method of claim 61, wherein said pathological condition is cancer.

63. The method of claim 61, wherein said cancer is melanoma.

64. The method of claim 61, further comprising contacting said sample to purified cancer associated antigen encoded by SEQ ID NO: 1, 3, 4, 8, 15, 19, 22 or 26.

65. A method for screening for possible presence of a pathological condition in a subject, comprising assaying a sample taken from said subject for expression of a nucleic acid molecule, the nucleotide sequence of which comprises SEQ ID NO: 1, 2, 3, 4, 8, 15, 19, 22 or 26, expression of said nucleic acid molecule being indicative of possible presence of said pathological condition.

66. The method of claim 65, wherein said pathological condition is cancer.

67. The method of claim 65, comprising determining expression via polymerase chain reaction.

68. The method of claim 65, comprising determining expression by contacting said sample with at least one of SEQ ID NO: 9, 10, 11, 12, 13, 14, 17, 18, 20, 21, 24, 25, 28 or 29.

69. A method for determining regression, progression of onset of a cancerous condition comprising monitoring a sample from a patient with said cancerous condition for a parameter selected from the group consisting of (i) a cancer associated antigen encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15, 19, 22 or 25, (ii) a peptide derived from said cancer associated antigen,

(iii) cytolytic T cells specific for said peptide and an MHC molecule with which it non-covalently complexes, and (iv) antibodies specific for said cancer associated antigen, wherein amount of said parameter is indicative of progression or regression or onset of said cancerous condition.

70. The method of claim 69, wherein said sample is a body fluid or exudate.

71. The method of claim 69, wherein said sample is a tissue.

72. The method of claim 69, comprising contacting said sample with an antibody which specifically binds with said protein or peptide.

73. The method of claim 72, wherein said antibody is labelled with a radioactive label or an enzyme.

74. The method of claim 72, wherein said antibody is a monoclonal antibody.

75. The method of claim 69, comprising amplifying RNA which codes for said protein.

76. The method of claim 75, wherein said amplifying comprises carrying out polymerase chain reaction.

77. The method of claim 69, comprising contacting said sample with a nucleic acid molecule which specifically hybridizes to a nucleic acid molecule which codes for or expresses said protein.

78. The method of claim 69, comprising assaying said sample for shed cancer associated antigen.

79. The method of claim 69, comprising assaying said sample for antibodies specific for said cancer associated antigen, by contacting said sample with said cancer associated antigen.

80. Method for screening for a cancerous condition comprising assaying a sample taken from a subject for an immunoreactive cell specific for a peptide derived from a cancer associated antigen encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15, 19, 22 or 26, complexed to an MHC molecule, presence of said immunoreactive cell being indicative of said cancerous condition.

81. An isolated nucleic acid molecule consisting of a nucleotide sequence defined by SEQ ID NO: 1, 2, 3, 8, 15, 19, 22 or 26.

82. Isolated nucleic acid molecule the complimentary sequence of which hydridizes, under stringent conditions, to the nucleotide sequence set forth in SEQ ID NO: 4, 5, 8, 15, 19, 22 or 26.

83. An isolated polypeptide comprising at least 9 consecutive amino acids set forth in SEQ ID NO: 5, 7, 16, 19, 23, 27, or 30.

84. The isolated polypeptide of claim 83, comprising at least 9 consecutive amino acids set forth in SEQ ID NO: 23 or 30.

85. The isolated polypeptide of claim 84, comprising t least 9 consecutive amino acids of the amino acid sequence set forth in SEQ ID NO: 23.

86. The isolated polypeptide of claim 85, comprising amino acids 102-111, 904-912 or 1262-1270 of SEQ ID NO: 23.

87. An isolated nucleic acid molecule which encodes the amino acid sequence of SEQ ID NO: 30.

88. An isolated nucleic acid molecule which encodes the isolated polypeptide of claim 86.

89. Expression vector comprising the isolated nucleic acid molecule of claim 88, operably linked to a promater.

<110> Jager, Dirk
Scanlan, Matthew
Gure, Ali
Jager, Elke
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Chen, Yao-tseng

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ggaagagata aggcctaggg aag 23

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ctgccttcga gcctgccatt gaaatgcaaa agtctgttcc aaataaagcc ttggaattga 180

agaatgaaca aacattgaga gcagatgaga tactcccatc agaatccaaa caaaaggact 240

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gtttacccaa ggctacacat caaaaagaaa tagataaaat aaatggaaaa ttagaagagt 360

ctcctgataa tgatggtttt ctgaaggctc cctgcagaat gaaagtttct atttcaacta 420

aagccttaga attgatggac atgcaaactt tcaaagcaga gcctcccgag aagccatctg 480

ccttcgagcc tgccattgaa atgcaaaagt ctgttccaaa taaagccttg gaattgaaga 540

atgaacaaac attgagagca gatcagatgt tcccttcaga atcaaaacaa aagaaggttg 600

aagaaaattc ttgggattct gagagtctcc gtgagactgt ttcacagaag gatgtgtgtg 660

tacccaaggc tacacatcaa aaagaaatgg ataaaataag tggaaaatta gaagattcaa 720

ctagcctatc aaaaatcttg gatacagttc attcttgtga aagagcaagg gaacttcaaa 780

aagatcactg tgaacaacgt acaggaaaaa tggaacaaat gaaaaagaag ttttgtgtac 840

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aatgggaaca agagctctgc agtgtgagat tgactttaaa ccaagcagaa gagaagagaa 960

gaaatgccga tatattaaat gaaaaaatta gggaagaatt aggaagaatc gaagagcagc 1020

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tgaacacatg tntcaaancg aacaagatna tgtgaacaaa cacactganc agcaggagtc 1800

tctagatcag aaattatttc aactacaaag caaaatatg tggcttcaac agcaattagt 1860

tcatgcacat aangaaagct gacaacaaaa gcaagataac aattgatntt cattntcttg 1920

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ccatttaaaa aacccgtata tttcaatatg gaaaaaaaaa anaaaaaaaa 2030

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Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala
20 25 30

Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn
35 40 45

Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln
50 55 60

Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr
65 70 75 80

Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His Gln Lys Glu
85 90 95

Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp Gly
100 105 110

Phe Leu Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys Ala
115 120 125

Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys
130 135 140

Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn
145 150 155 160

Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln Met
165 170 175

Phe Pro Ser Glu Ser Lys Gln Lys Lys Val Gln Glu Asn Ser Trp Asp
180 185 190

Ser Glu Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val Pro
195 200 205

Lys Ala Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu Glu
210 215 220

Asp Ser Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys Glu
225 230 235 240

Arg Ala Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly Lys
245 250 255

Met Glu Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu Ser
260 265 270

Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys Trp

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        275                 280                 285

Glu Gln Glu Leu Cys Ser Val Arg Leu Thr Leu Asn Gln Glu Glu Glu
    290                 295                 300

Lys Arg Arg Asn Ala Asp Ile Leu Asn Glu Lys Ile Arg Glu Glu Leu
305                 310                 315                 320

Gly Arg Ile Glu Glu Gln His Arg Lys Glu Leu Glu Val Lys Gln Gln
                325                 330                 335

Leu Glu Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val Glu
            340                 345                 350

Ser Asn Leu Asn Gln Val Ser His Thr His Glu Asn Glu Asn Tyr Leu
        355                 360                 365

Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys Leu
    370                 375                 380

Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys Tyr
385                 390                 395                 400

Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln Met
                405                 410                 415

Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln Tyr
            420                 425                 430

Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr Ser
        435                 440                 445

Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile Glu
    450                 455                 460

Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln Ile
465                 470                 475                 480

Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly Asp
                485                 490                 495

Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Asp Ile
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<400> 18
cacacaaagc ttctaggatt tggcacagcc agag 34

<210> 19
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            20                  25                  30
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Pro Arg Pro Ala Gly Pro Ala Arg Arg Gln Phe Gln Ala Ala Ser Leu
        35                  40                  45

Leu Thr Arg Gly Trp Gly Arg Ala Trp Pro Trp Lys Gln Ile Leu Lys
    50                  55                  60

Glu Leu Asp Glu Cys Tyr Glu Arg Phe Ser Arg Glu Thr Asp Gly Ala
65                  70                  75                  80

Gln Lys Arg Arg Met Leu His Cys Val Gln Arg Ala Leu Ile Arg Ser
                85                  90                  95

Gln Glu Leu Gly Asp Glu Lys Ile Gln Ile Val Ser Gln Met Val Glu
            100                 105                 110

Leu Val Glu Asn Arg Thr Arg Gln Val Asp Ser His Val Glu Leu Phe
        115                 120                 125

Glu Ala Gln Gln Glu Leu Gly Asp Thr Val Gly Asn Ser Gly Lys Val
    130                 135                 140

Gly Ala Asp Arg Pro Asn Gly Asp Ala Val Ala Gln Ser Asp Lys Pro
145                 150                 155                 160

Asn Ser Lys Arg Ser Arg Arg Gln Arg Asn Asn Glu Asn Arg Glu Asn
                165                 170                 175

Ala Ser Ser Asn His Asp His Asp Asp Gly Ala Ser Gly Thr Pro Lys
            180                 185                 190

Glu Lys Lys Ala Lys Thr Ser Lys Lys Lys Lys Arg Ser Lys Ala Lys
        195                 200                 205

Ala Glu Arg Glu Ala Ser Pro Ala Asp Leu Pro Ile Asp Pro Asn Glu
    210                 215                 220

Pro Thr Tyr Cys Leu Cys Asn Gln Val Ser Tyr Gly Glu Met Ile Gly
225                 230                 235                 240

Cys Asp Asn Asp Glu Cys Pro Ile Glu Trp Phe His Phe Ser Cys Val
                245                 250                 255

Gly Leu Asn His Lys Pro Lys Gly Lys Trp Tyr Cys Pro Lys Cys Arg
            260                 265                 270

Gly Glu Asn Glu Lys Thr Met Asp Lys Ala Leu Glu Lys Ser Lys Lys
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Glu Arg Ala Tyr Asn Arg
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<210> 22
<211> 4115
<212> DNA
<213> Homo sapiens
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<212> PRT
<213> Homo sapiens
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Lys Arg Thr Ala Leu His Trp Ala Cys Val Asn Gly His Glu Glu Val
            20                  25                  30

Val Thr Phe Leu Val Asp Arg Lys Cys Gln Leu Asp Val Leu Asp Gly
        35                  40                  45

Glu His Arg Thr Pro Leu Met Lys Ala Leu Gln Cys His Gln Glu Ala
    50                  55                  60

Cys Ala Asn Ile Leu Ile Asp Ser Gly Ala Asp Ile Asn Leu Val Asp
65                  70                  75                  80

Val Tyr Gly Asn Met Ala Leu His Tyr Ala Val Tyr Ser Glu Ile Leu
                85                  90                  95

Ser Val Val Ala Lys Leu Leu Ser His Gly Ala Val Ile Glu Val His
            100                 105                 110

Asn Lys Ala Ser Leu Thr Pro Leu Leu Leu Ser Ile Thr Lys Arg Ser
        115                 120                 125

Glu Gln Ile Val Glu Phe Leu Leu Ile Lys Asn Ala Asn Ala Asn Ala
    130                 135                 140

Val Asn Lys Tyr Lys Cys Thr Ala Leu Met Leu Ala Val Cys His Gly
145                 150                 155                 160

Ser Ser Glu Ile Val Gly Met Leu Leu Gln Gln Asn Val Asp Val Phe
                165                 170                 175

Ala Ala Asp Ile Cys Gly Val Thr Ala Glu His Tyr Ala Val Thr Cys
            180                 185                 190

Gly Phe His His Ile His Glu Gln Ile Met Glu Tyr Ile Arg Lys Leu
        195                 200                 205

Ser Lys Asn His Gln Asn Thr Asn Pro Glu Gly Thr Ser Ala Gly Thr
    210                 215                 220

Pro Asp Glu Ala Ala Pro Leu Ala Glu Arg Thr Pro Asp Thr Ala Glu
225                 230                 235                 240

Ser Leu Val Glu Lys Thr Pro Asp Glu Ala Ala Pro Leu Val Glu Arg
                245                 250                 255

Thr Pro Asp Thr Ala Glu Ser Leu Val Glu Lys Thr Pro Asp Glu Ala
            260                 265                 270

Ala Ser Leu Val Glu Gly Thr Ser Asp Lys Ile Gln Cys Leu Glu Lys
        275                 280                 285

Ala Thr Ser Gly Lys Phe Glu Gln Ser Ala Glu Glu Thr Pro Arg Glu
    290                 295                 300

Ile Thr Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Pro Ala
305                 310                 315                 320

Lys Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Asp Thr Pro
                325                 330                 335

Arg Glu Ile Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp
            340                 345                 350

Ala Ala Lys Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr
        355                 360                 365

Pro Val Lys Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys
    370                 375                 380

Val Leu Glu Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu
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385 390 395 400

Ser Ser Thr Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser
405 410 415

Lys Gln Glu Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe
420 425 430

Glu Ser Ser Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln
435 440 445

Lys Val Met Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro
450 455 460

Ser Ala Phe Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys
465 470 475 480

Ala Phe Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe
485 490 495

Pro Pro Glu Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser
500 505 510

Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys
515 520 525

Ala Thr His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu
530 535 540

Ser Pro Asn Lys Asp Gly Leu Leu Lys Ala Thr Cys Gly Met Lys Val
545 550 555 560

Ser Ile Pro Thr Lys Ala Leu Glu Leu Lys Asp Met Gln Thr Phe Lys
565 570 575

Ala Glu Pro Pro Gly Lys Pro Ser Ala Phe Glu Pro Ala Thr Glu Met
580 585 590

Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr
595 600 605

Trp Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr
610 615 620

Glu Glu Asn Ser Trp Asp Thr Glu Ser Leu Cys Glu Thr Val Ser Gln
625 630 635 640

Lys Asp Val Cys Leu Pro Lys Ala Ala His Gln Lys Glu Ile Asp Lys
645 650 655

Ile Asn Gly Lys Leu Glu Gly Ser Pro Val Lys Asp Gly Leu Leu Lys
660 665 670

Ala Asn Cys Gly Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu
675 680 685

Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala
690 695 700

Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu
705 710 715 720

Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser
725 730 735

Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser
740 745 750

Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr
755 760 765

His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro

770 775 780

Asp Asn Asp Gly Phe Leu Lys Ala Pro Cys Arg Met Lys Val Ser Ile
785 790 795 800

Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu
805 810 815

Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys
820 825 830

Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg
835 840 845

Ala Asp Gln Met Phe Pro Ser Glu Ser Lys Gln Lys Lys Val Glu Glu
850 855 860

Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu Thr Val Ser Gln Lys Asp
865 870 875 880

Val Cys Val Pro Lys Ala Thr His Gln Lys Glu Met Asp Lys Ile Ser
885 890 895

Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser Lys Ile Leu Asp Thr Val
900 905 910

His Ser Cys Glu Arg Ala Arg Glu Leu Gln Lys Asp His Cys Glu Gln
915 920 925

Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys Phe Cys Val Leu Lys
930 935 940

Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln
945 950 955 960

Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu Thr Leu Asn
965 970 975

Gln Glu Glu Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn Glu Lys Ile
980 985 990

Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His Arg Lys Glu Leu Glu
995 1000 1005

Val Lys Gln Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu
1010 1015 1020

Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser His Thr His Glu Asn
1025 1030 1035 1040

Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala
1045 1050 1055

Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
1060 1065 1070

Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
1075 1080 1085

Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg
1090 1095 1100

Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr
1105 1110 1115 1120

Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu
1125 1130 1135

Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp
1140 1145 1150

His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His

1155 1160 1165

Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser
1170 1175 1180

Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala
1185 1190 1195 1200

Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp
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Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln
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Arg Glu Thr Gln Cys Gln Met Lys Gln Ala Glu His Met Tyr Gln Asn
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Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp
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Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln
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Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile
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Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu
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Gln Thr Val Glu Phe Leu Leu Thr Lys Asn Ala Asn Ala Asn Ala Phe
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Asn Glu Ser Lys Cys Thr Ala Leu Met Leu Ala Ile Cys Glu Gly Ser
    50                  55                  60

Ser Glu Ile Val Gly Met Leu Leu Gln Gln Asn Val Asp Val Phe Ala
65                  70                  75                  80

Glu Asp Ile His Gly Ile Thr Ala Glu Arg Tyr Ala Ala Ala Arg Gly
                85                  90                  95

Val Asn Tyr Ile His Gln Gln Leu Leu Glu His Ile Arg Lys Leu Pro
            100                 105                 110

Lys Asn Pro Gln Asn Thr Asn Pro Glu Gly Thr Ser Thr Gly Thr Pro
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Asp Glu Ala Ala Pro Leu Ala Glu Arg Thr Pro Asp Thr Ala Glu Ser
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Leu Leu Glu Lys Thr Pro Asp Glu Ala Ala Arg Leu Val Glu Gly Thr
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Ser Ala Lys Ile Gln Cys Leu Gly Lys Ala Thr Ser Gly Lys Phe Glu
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Gln Ser Thr Glu Glu Thr Pro Arg Lys Ile Leu Arg Pro Thr Lys Glu
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Thr Ser Glu Lys Phe Ser Trp Pro Ala Lys Glu Arg Ser Arg Lys Ile
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Thr Trp Glu Glu Lys Glu Thr Ser Val Lys Thr Glu Cys Val Ala Gly
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Val Thr Pro Asn Lys Thr Glu Val Leu Glu Lys Gly Thr Ser Asn Met
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Ile Ala Cys Pro Thr Lys Glu Thr Ser Thr Lys Ala Ser Thr Asn Val
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Asp Val Ser Ser Val Gln Pro Ile Phe Ser Leu Phe Gly Thr Arg Thr
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Thr Lys Ile Ile Ser Lys Ser Ala Ala Gln Asn Tyr Thr Cys Leu Pro
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Asp Ala Thr Tyr Gln Lys Asp Ile Lys Thr Ile Asn His Lys Ile Glu
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Ser Trp Asp Ser Gly Ser Leu Phe Glu Ser Ser Ala Lys Thr Gln Val
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Cys Ile Pro Glu Ser Met Tyr Gln Lys Val Met Glu Ile Asn Arg Glu
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Val Glu Glu Leu Pro Glu Lys Pro Ser Ala Phe Lys Pro Ala Val Glu
370 375 380

Met Gln Lys Thr Val Pro Asn Lys Ala Phe Gln Leu Lys Asn Glu Gln
385 390 395 400

Thr Leu Arg Ala Ala Gln Met Phe Pro Ser Glu Ser Lys Gln Lys Asp
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Asp Glu Glu Asn Ser Trp Asp Ser Glu Ser Pro Cys Glu Thr Val Ser
420 425 430

Gln Lys Asp Val Tyr Leu Pro Lys Ala Thr His Gln Lys Glu Phe Asp
435 440 445

Thr Leu Ser Gly Lys Leu Glu Glu Ser Pro Val Lys Asp Gly Leu Leu
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Lys Pro Thr Cys Gly Arg Lys Val Ser Leu Pro Asn Lys Ala Leu Glu
465 470 475 480

Leu Lys Asp Arg Glu Thr Phe Lys Ala Glu Ser Pro Asp Lys Asp Gly
485 490 495

Leu Leu Lys Pro Thr Cys Gly Arg Lys Val Ser Leu Pro Asn Lys Ala
500 505 510

Leu Glu Leu Lys Asp Arg Glu Thr Leu Lys Ala Glu Ser Pro Asp Asn
515 520 525

Asp Gly Leu Leu Lys Pro Thr Cys Gly Arg Lys Val Ser Leu Pro Asn

530 535 540

Lys Ala Leu Glu Leu Lys Asp Arg Glu Thr Phe Lys Ala Ala Gln Met
545 550 555 560

Phe Pro Ser Glu Ser Lys Gln Lys Asp Asp Glu Glu Asn Ser Trp Asp
565 570 575

Phe Glu Ser Phe Leu Glu Thr Leu Leu Gln Asn Asp Val Cys Leu Pro
580 585 590

Lys Ala Thr His Gln Lys Glu Phe Asp Thr Leu Ser Gly Lys Leu Glu
595 600 605

Glu Ser Pro Asp Lys Asp Gly Leu Leu Lys Pro Thr Cys Gly Met Lys
610 615 620

Ile Ser Leu Pro Asn Lys Ala Leu Glu Leu Lys Asp Arg Glu Thr Phe
625 630 635 640

Lys Ala Glu Asp Val Ser Ser Val Glu Ser Thr Phe Ser Leu Phe Gly
645 650 655

Lys Pro Thr Thr Glu Asn Ser Gln Ser Thr Lys Val Glu Glu Asp Phe
660 665 670

Asn Leu Thr Thr Lys Glu Gly Ala Thr Lys Thr Val Thr Gly Gln Gln
675 680 685

Glu Arg Asp Ile Gly Ile Ile Glu Arg Ala Pro Gln Asp Gln Thr Asn
690 695 700

Lys Met Pro Thr Ser Glu Leu Gly Arg Lys Glu Asp Thr Lys Ser Thr
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Ser Asp Ser Glu Ile Ile Ser Val Ser Asp Thr Gln Asn Tyr Glu Cys
725 730 735

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740 745 750

Ile Glu Glu Ser Pro Glu Lys Pro Ser His Phe Glu Pro Ala Thr Glu
755 760 765

Met Gln Asn Ser Val Pro Asn Lys Gly Leu Glu Trp Lys Asn Lys Gln
770 775 780

Thr Leu Arg Ala Asp Ser Thr Thr Leu Ser Lys Ile Leu Asp Ala Leu
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Pro Ser Cys Glu Arg Gly Arg Glu Leu Lys Lys Asp Asn Cys Glu Gln
805 810 815

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Lys Ala Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu Pro Leu Asn
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Gln Glu Glu Glu Lys Arg Arg Asn Val Asp Ile Leu Lys Glu Lys Ile
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Arg Pro Glu Glu Gln Leu Arg Lys Lys Leu Glu Val Lys His Gln Leu
885 890 895

Glu Gln Thr Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val Thr Ser
900 905 910

Asn Leu Asn Gln Val Ser His Thr His Glu Ser Glu Asn Asp Leu Phe

915 920 925

His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys Leu Glu
930 935 940

Val Ala Thr Leu Lys His Gln His Gln Val Lys Glu Asn Lys Tyr Phe
945 950 955 960

Glu Asp Ile Lys Ile Leu Gln Glu Lys Asn Ala Glu Leu Gln Met Thr
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Leu Lys Leu Lys Gln Lys Thr Val Thr Lys Arg Ala Ser Gln Tyr Arg
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Arg Pro Ser Pro Phe Ser Gln Leu Val Tyr Thr Ser Asn Asp Ser Tyr
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Ile Val His Ser Gly Asp Leu Arg Lys Ile His Lys Ala Ala Ser Arg
35 40 45

Gly Gln Val Arg Lys Leu Glu Lys
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